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Editorial

EDITORIAL

Testicular Cancer as a Model for Understanding the Impact of Evolving Treatment Strategies on the Long-Term Health of Cancer Survivors

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Over the last century, radiotherapy has been used successfully to treat early stage testicular cancer, particularly seminomas. With the development of cisplatin-based chemotherapy regimens in the 1970s for advanced disease and nonseminomas, testicular cancer became one of the most curable malignancies and a defining achievement in oncology (1). This favorable prognosis combined with the relatively young age at testicular cancer diagnosis have made the long-term health of survivors a high clinical and research priority as well as a driving force behind further treatment refinements.

Not long after the introduction of cisplatin-based chemotherapy, population-based registry studies emerged as an invaluable tool for quantifying long-term health risks among cancer survivors, particularly the risk of subsequent malignant neoplasms. Although most registries lack detailed clinical and treatment data, they provide the large sample size and systematic, long-term follow-up that typically are absent from randomized controlled trials, thus offering critical contributions toward comprehensive understanding of survivors' long-term health. Early registry-based studies of testicular cancer survivors revealed increased risks of leukemia, sarcoma, and cancers of the gastrointestinal and urogenital tracts, which were largely attributed to treatment exposures (2–5). Most of these findings subsequently have been confirmed in more detailed studies of patients with testicular or other cancers, such as the dose-response relationships reported for platinum compounds with therapy-related acute myeloid leukemia (tAML) (6,7) and for radiotherapy with gastrointestinal cancers (8–10).

In their article published in this issue of *JNCI Cancer Spectrum*, Milano and colleagues (11) leveraged the data from nine US population-based cancer registries from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program to characterize subsequent malignant neoplasm risk among 24 900 testicular cancer survivors during 1973–2014. Major findings from previous large-scale European and US studies were confirmed in this report, most notably the excess risks of sarcoma, gastrointestinal cancers, and bladder cancer among patients treated with initial radiotherapy, and of sarcoma, gastrointestinal cancers, and tAML among patients treated with initial chemotherapy.

Changes in clinical approaches to cancer treatment offer important opportunities but also present major challenges to advancing understanding of risks for subsequent malignant neoplasms, as exemplified in the current report by Milano and colleagues (11). Over the last several decades, treatment for testicular cancer has continued to evolve in an effort to further improve patient outcomes, particularly by reducing use of adjuvant radiotherapy for early stage disease, reducing doses and volumes for patients who do receive radiotherapy, and increasing use of adjuvant chemotherapy (1). Although lower radiotherapy exposures ultimately are expected to reduce risk of subsequent malignant neoplasms, Milano and colleagues (11) report no change in risk for patients treated more recently, likely because of an insufficient amount of follow-up time in light of the 5-year to more than 20-year latency period typically expected for the development of radiotherapy-related subsequent malignant neoplasms. These same challenges are impeding timely, accurate assessments of the impacts of changes in radiotherapy approaches for other patient populations, such as those with Hodgkin lymphoma (12), childhood cancer (13), or prostate cancer (14).

Given that studies of late adverse effects of treatment by definition are focused on patients treated in the past, how can we make the results of these studies relevant for patients treated today? One opportunity is to conduct dose-response studies with detailed clinical data (15), so that the impact of changes in dose on subsequent malignant neoplasm risk can be estimated. Admittedly, radiation dose-response analyses alone are likely to prove incomplete based on emerging evidence that not just the dose but also the volume of tissue irradiated may impact subsequent malignant neoplasm risk (16) and also that there may be striking joint effects between radiotherapy and systemic

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therapy exposures for some outcomes (17–19). However, at the current time such analyses still provide a strong basis for risk projection. Another opportunity is to accelerate research on late effects through international collaboration (20). Rather than waiting to begin surveillance for late effects and being forced to rely on decades-old clinical data, establishment of consortia to collect data across many study centers for recently or currently treated patients will enable more effective and timely assessments of risks after the minimal sufficient latency period has occurred.

The excess risks of solid tumors after both radiotherapy and chemotherapy reported by Milano and colleagues (11) also emphasize two additional key issues. First, the results underscore the continued importance of identifying optimal long-term screening strategies for testicular cancer survivors. Despite facing elevated risks for subsequent malignant neoplasms and a number of other adverse health effects following treatment, testicular cancer survivors currently are advised to adhere to general population disease prevention and screening practices (21). The lack of evidence- or consensus-based long-term follow-up guidelines is an impediment to maximizing the long-term health and well-being of testicular cancer survivors. Second, the results highlight accumulating evidence that certain types of chemotherapy increase risks not just for tAML and cancers within organs that are directly involved in the metabolism of these agents [eg, bladder (22)] but also for sarcomas and cancers of the pancreas, lung, thyroid, and breast (9,17,23–29). The apparent diversity of tissues that appear to be at risk combined with the range of chemotherapy types that have been implicated—from platinum-based compounds and alkylating agents to anthracyclines—emphasizes the importance of quantifying chemotherapy-related solid cancer risks and elucidating the underlying mechanisms of carcinogenesis.

The medical community must continue to prioritize research that advances understanding of treatment-related adverse effects and improves the long-term health of cancer survivors. Registry-based studies such as that from Milano and colleagues (11) offer critical contributions toward these goals because of their large sample size and systematic, long-term follow-up. Optimally, observations from such studies would be combined with clinical trials and detailed dose-response studies, as well as other advances in medical research, such as the utilization of genomic technologies to identify cancer survivors who are particularly susceptible to the development of treatment-related adverse effects (30,31). Only then will the impact of treatment refinements and the optimal approach to maximize the long-term health of cancer survivors be truly understood.

Note

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